Theoretical study of the first step of SPLET mechanism: O—H bond cleavage in the mono-substituted benzoic acids

Martin Michalík, Peter Škorňa, Vladimír Lukeš

Department of Chemical Physics, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia
xmichalikm@stuba.sk

Abstract: The first step of SPLET mechanism in solution phase for 15 benzoic acid derivatives was studied from the thermodynamic point of view. For this purpose, proton affinities (PAs) of corresponding carboxylate or phenoxide anions were computed by means of DFT method employing B3LYP and M062X functionals with 6-311++G** basis set and SMD or IEF-PCM solvent model. The substituent effect on PAs was analyzed in terms of Hammett constants, σ_p. Found dependences exhibit satisfactory linearity and enable quick estimation of solution phase PAs from the Hammett constants.

Keywords: Proton affinity, B3LYP, M062X, IEF-PCM, SMD, benzoic acid derivatives

Introduction

Protonation or deprotonation is the first step in many important chemical reactions. The ability of a molecule to abstract a proton is characterized, from thermodynamical point of view, by proton affinity (PA) of the corresponding anion. PA is useful as a measure of the correlations between the acidity of organic compounds and their structure. Comparison of the PA values with pKa values of the respective acids in solution gives information about the solvation effects on the acidity of studied molecules. From the practical point of view, it can help to rationalize the fragmentation pathways of compounds of interest.

Like numerous other natural phenolic compounds, hydroxybenzoic acids exhibit antioxidative properties as free radical scavengers and metal ion chelators (Andjelkovic, 2006). The structure of phenolic compounds, especially the number and position of OH groups, seems to play the crucial role in their antioxidant, antiproliferative, cytotoxic and enzyme inhibition activities (Pietta, 2000). Many of the health-promoting activities of phenolic compounds are ascribed to their antioxidant activities as well as to their ability to modify cellular signaling pathways. Most ingested flavonoids are extensively degraded to various hydroxybenzoic acids, some of which possess high radical scavenging ability (Cuvelier, 1992; Duenas, 2011).

The hydroxybenzoic acids occur mainly in the form of glycosides and are rarely free in edible plants, such as rosaceous fruits (strawberry, blackberry, blackcurrant and raspberry), potatoes, black radishes, grape seeds, onions, wines, and teas. As conjugates, hydroxybenzoics are components of plant complex polyphenolic structures, such as lignins and hydrolysable tannins (Barberan, 2000; Herrmann, 1989; Manach, 2004). Hydroxybenzoic acids are present in red wine as cofactors of the anthocyanin pigments (Zhang, 2015).

In this work we investigate the first step of sequential proton-loss electron-transfer (SPLET) mechanism.

$$ArX{-}H \rightarrow ArX^- + H^+ \qquad (1)$$

The reaction enthalpy of this step is proton affinity (PA). From the thermodynamic point of view, entering SPLET mechanism is the most probable process in water, where PAs are frequently considerably lower than bond dissociation enthalpies (Klein, 2009). PA values can be experimentally or theoretically determined. Experimental determination is possible only in the gas phase. Proton afinity also depends on the position of substituents at the aromatic ring (Bordwell et al., 1994; Klein and Lukeš, 2006).

Because the SPLET mechanism is relevant mainly in the solution phase, the main aim of this work is to calculate the O—H proton affinities of mono-substituted benzoic acids in solution phase. This paper extends the work commenced in Škorňa et al., 2015. Reliability of the obtained values was assessed by means of their comparison with available experimental and theoretical data. Furthermore, the substituent effect was assessed for the reaction enthalpy of a set of 14 *para*-substituted benzoic acids.

Computational details

The calculations were carried out using the Gaussian 09 program package (Frisch et al., 2009). All geometries were fully optimized by minimizing the energy with respect to all geometrical variables using DFT method employing the widely used B3LYP (Becke,1988; Lee et al., 1988; Frisch et al., 2009) and M062X functional (Zhao et al., 2008) without any constraints (energy cut-off of 10^{-5} kJ · mol^{-1} , final RMS energy gradient below 0.01 kJ · mol^{-1} · Å^{-1}). For species having several conformers all the conformers were investigated and the conformers with the lowest electronic energy were used. Calculations were performed in the standard 6-311++G** basis set of Pople (Krishnan et al., 1980; McLean and Chandler, 1980; Curtiss et al., 1995). This level of theory was found to outperform more expensive wave function-based methods for calculations of absolute proton affinities, thus comforting us in this choice. (Dumont, 2009). The optimized structures were confirmed to be true minima by the vibration analysis (no imaginary frequency). All enthalpies were calculated for 298.15 K. Proton affinities (PA) were calculated from the total enthalpies as follows:

$$PA = H(ArX^-) + H(H^+) - H(ArX—H) \quad (2)$$

The influence of the water as a solvent was approximated by the continuum Solvation Model based on the quantum mechanical charge Density, SMD (Marenich et al., 2009) of a solute molecule interacting with a continuum description of the solvent and Integral Equation Formalism Polarized Continuum Model, IEF-PCM (Cances et al., 1997). Total proton enthalpies in water reached the following values: –984.6 kJ · mol^{-1} (B3LYP/IEF-PCM), –1049.2 (B3LYP/SMD), –985.7 (M062X/IEF-PCM) and –1049.5 kJ · mol^{-1} (M062X/SMD). Available experimental value of proton solvation enthalpy is its hydration enthalpy, $\Delta_{hydr}H(H^+)$ = –1090 kJ · mol^{-1} (Atkins, 1998). For hydroxybenzoic acids full torsion scans of carboxyl group were performed with 15 ° steps and subsequent geometry relaxation.

Results and discussion

Proton affinities of hydroxybenzoic acid

The term *protomers* has been suggested for species differing exclusively in the binding site of a proton (Galaverna, 2015). Figure 1 depicts the stable protomers of *ortho*- (salicylic acid) and *meta*- substituted benzoic acid. Theoretical calculations in solvent, using DFT level of theory with IEF-PCM or SMD models was employed to indicate the energy difference of the stable species. Negligible difference at the level of standard deviation (0.1 kJ · mol^{-1}) was found for *para*-hydroxy protomers having O—H and C═O bonds in anti or sym position to each other. In gas phase a similar difference (0.2 kJ · mol^{-1}) was found (Aarset, 2008). Despite the difference in geometries, carboxyl group remained coplanar with the phenyl ring in all studied isomers. To evaluate energy barrier for the rotation of the carboxyl group, torsion scans were performed with 15 ° steps and subsequent geometry relaxations, starting from the geometry of the energy minima, depicted in Fig. 3. The highest energy barrier (nearly 40 kJ · mol^{-1}) was observed in *ortho*-hydroxy benzoic acid. *Para*-hydroxy isomer shows 27 kJ · mol^{-1} energy barrier and *meta*-hydroxy benzoic acid has the lowest 21 kJ · mol^{-1} energy barrier.

The two viable ways of deprotonating hydroxybenzoic acids are presented in Figure 1.

The calculated PA values are summarized in Table 1. Only in the case of *ortho*-isomer, OH group deprotonation was found to be thermodynamically preferred. In gas phase hydroxyl group deprotonation was favored in *para*-isomer (Škorňa, 2015). Chen et al. found (B3LYP/6-311++G**) for phenoxide anion of salicylic acid in water the PA value of 194 kJ · mol^{-1}. Considering that proton can be abstracted from any site, PAs of these isomers were in the following descending order: *ortho*- < *meta*- < *para*-, which can be correlated with known experimental pKa values (2.9, 4.0, 4.5) (Abramson 2013).

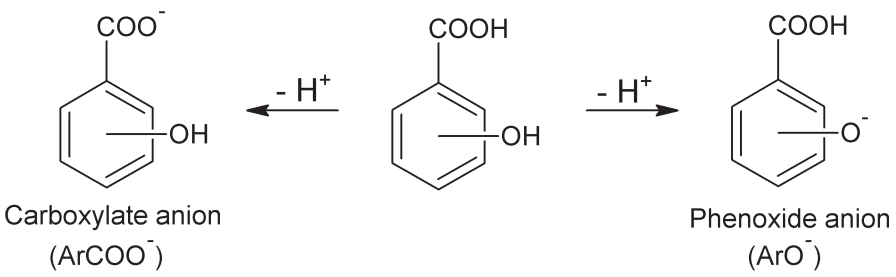
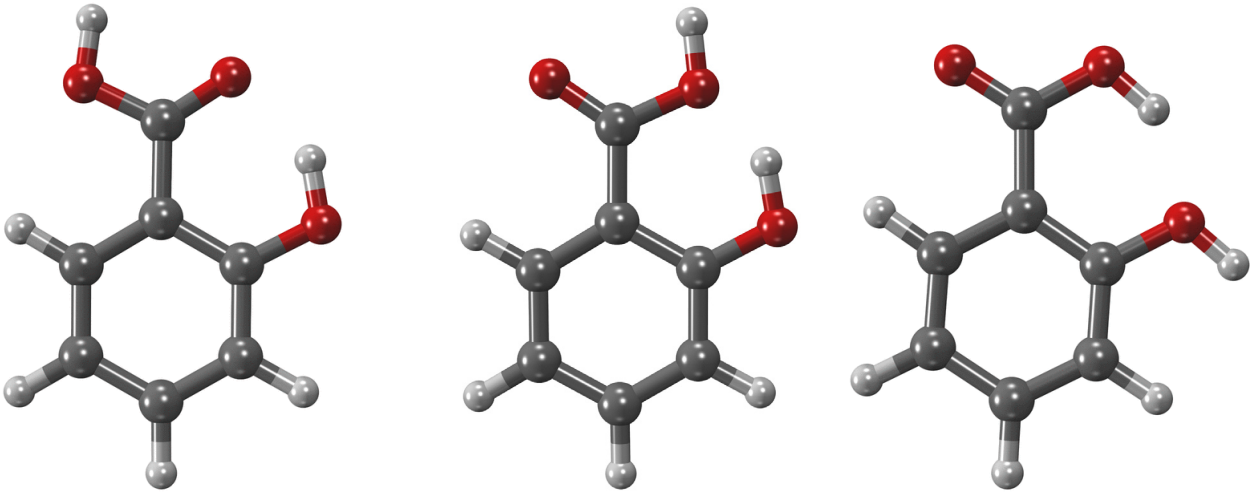


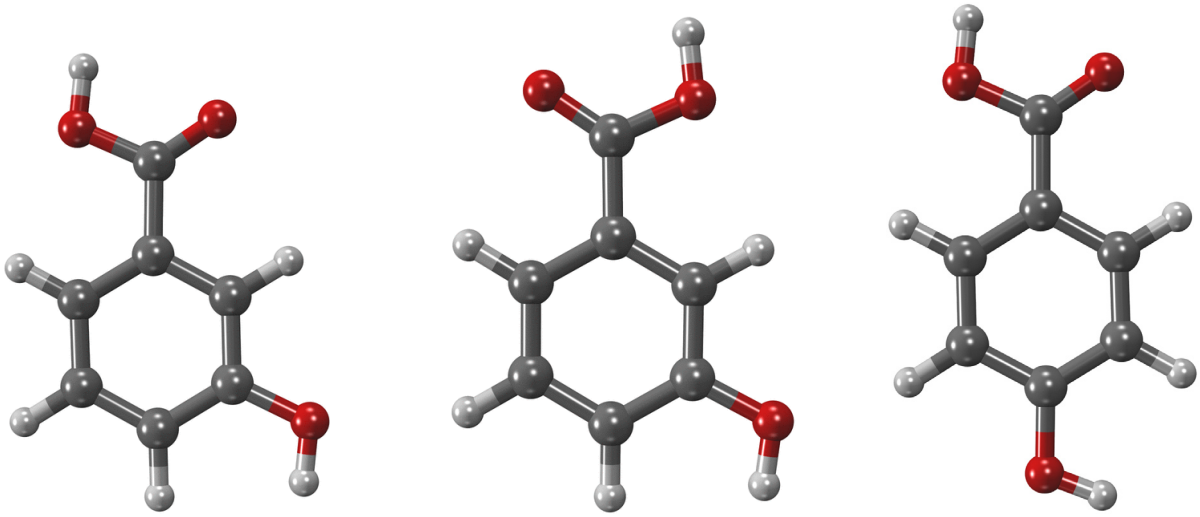
Fig. 1. Formation of deprotonated species from hydroxybenzoic acid.

Tab. 1. B3LYP and M062X/6-311++G** proton affinities of *ortho*-, *meta*- and *para*-substituted hydroxybenzoic adic using IEF-PCM and SMD solvent models.

Functional/solvent model	Carboxylate anion PA/kJ·mol^{-1}			Phenoxide anion PA/kJ·mol^{-1}		
	Ortho	*Meta*	*Para*	*Ortho*	*Meta*	*Para*
B3LYP/IEF-PCM	224	194	200	176	227	208
M062X/IEF-PCM	223	190	195	165	226	208
B3LYP/SMD	137	112	119	110	154	140
M062X/SMD	129	107	113	95	154	139



Ortho-1, ΔE = 0 kJ mol^{-1} *Ortho-2*, ΔE = 9 kJ mol^{-1} *Ortho-3*, ΔE = 19 kJ mol^{-1}



Meta-1, ΔE = 0 kJ mol^{-1} *Meta-2*, ΔE = 1 kJ mol^{-1} *Para*

Fig. 2. Stable isomers of hydroxybenzoic acid, ΔE represents the energy difference between the protomers.

Para-substituted benzoic acids

Tables 2 and 3 present proton affinities of 14 *para*-substituted benzoic acid derivatives in the aqueous solution. Employing IEF-PCM and SMD solvation models, the found PAs were in the range up to 33 kJ · mol^{-1} for both solvation models. Unfortunately, experimental PAs for *para*-substituted benzoic acids are rather scarce and limited to the gas phase only. In comparison with the theoretical gas phase PA data presented by Škorňa et al., our calculations are lower by ca 1200 kJ · mol^{-1}. Gas phase PA values are in the wide range from

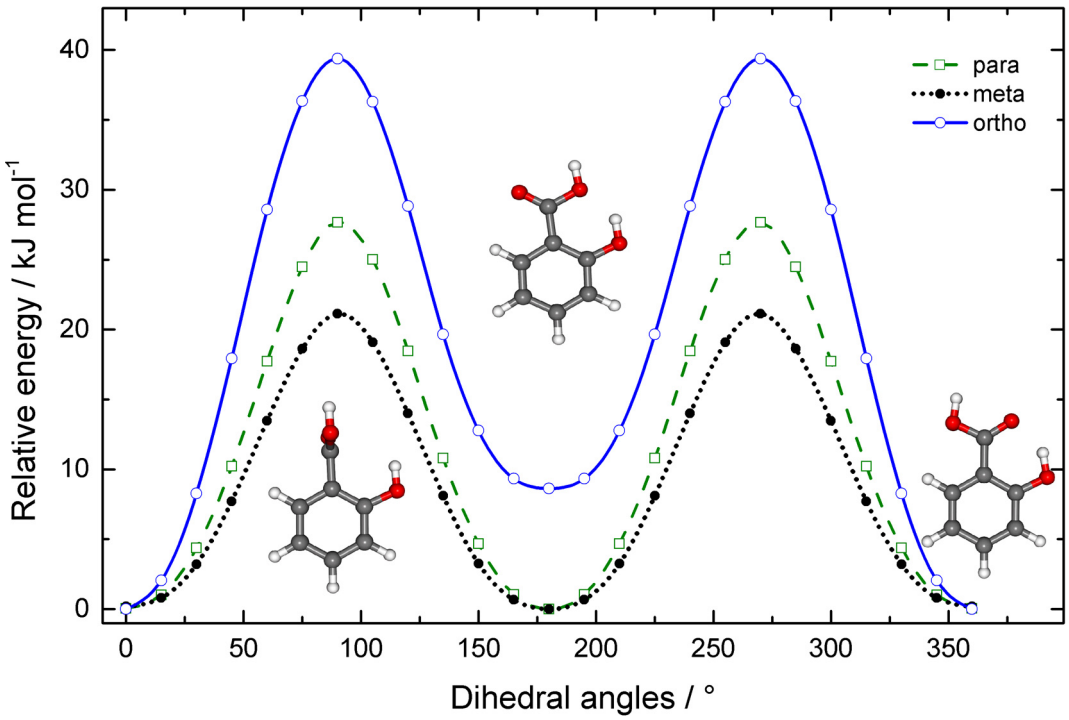


Fig. 3. Relative energies (ΔE) and energy barriers for the torsion scans performed (15 ° steps).

1363 kJ · mol^{-1} (*para*-NO_2) to 1438 kJ · mol^{-1} (*para*-NMe_2). It is well-known fact that solvents, in contrast to the gas phase, tend to attenuate PA values with the increase of their polarity. Moreover gas phase PAs are significantly higher than the solution phase ones, which is mainly due to the large enthalpy of H^+ hydration (Klein, 2009; Taft, 1983). Nevertheless the electron-donating or electron-withdrawing nature of the substituent has a non-negligible influence on thermochemical properties. In comparison with non-substituted benzoic acid, electron-donating substituents induce the PA increase. On the other hand, electron-withdrawing groups decrease PA values, thus increasing the acidity of the carboxyl group. Such trend is clearly obeyed by substituents with strong effects and is

Tab. 2. M062X/6-311++G** proton affinities of *para*-substituted benzoic acid derivatives using IEF-PCM and SMD solvent models and the corresponding Hammett constants, σ_p.

Substituent	M062X/IEF-PCM		M062X/SMD		σ_p
	PA/kJ·mol^{-1}	ΔPA/kJ·mol^{-1}	PA/kJ·mol^{-1}	ΔPA/kJ·mol^{-1}	
H	191	0	111	0	0
NMe_2	203	12	119	8	–0.83
NH_2	201	10	119	8	–0.66
MeO	196	5	114	3	–0.27
t-Bu	194	3	113	2	–0.2
Me	194	3	112	1	–0.17
Ph	191	0	110	–1	–0.01
F	188	–3	109	–2	0.06
Br	186	–5	107	–4	0.23
Cl	186	–5	107	–4	0.23
MeCO	184	–7	106	–5	0.5
CF_3	181	–10	104	–7	0.54
CN	179	–12	103	–8	0.66
$MeSO_2$	178	–13	102	–9	0.72
NO_2	176	–15	100	–11	0.78

Tab. 3. B3LYP/6-311++G** proton affinities of *para*-substituted benzoic acid derivatives using IEF-PCM and SMD solvent models and the corresponding Hammett constants, σ_p.

Substituent	B3LYP/IEF-PCM		B3LYP/SMD		σ_p
	PA/kJ·mol^{-1}	ΔPA/kJ·mol^{-1}	PA/kJ·mol^{-1}	ΔPA/kJ·mol^{-1}	
H	195	0	116	0	0
NMe_2	210	15	126	10	–0.83
NH_2	207	12	125	9	–0.66
MeO	201	6	120	4	–0.27
t-Bu	198	3	118	2	–0.2
Me	198	3	118	2	–0.17
Ph	195	0	116	0	–0.01
F	192	–3	114	–2	0.06
Br	190	–5	112	–4	0.23
Cl	190	–5	112	–4	0.23
MeCO	187	–8	110	–6	0.5
CF_3	185	–10	109	–7	0.54
CN	182	–13	107	–9	0.66
$MeSO_2$	183	–12	105	–11	0.72
NO_2	177	–18	104	–12	0.78

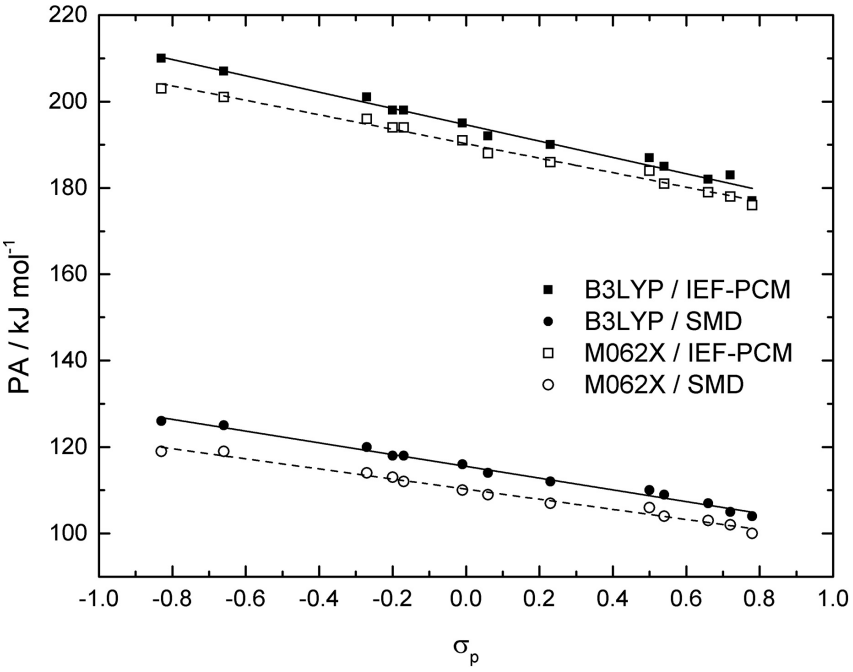


Fig 4. Correlation of the PAs with Hammett constants, σ_p.

evident from the Tables 2 and 3 displaying also ΔPA values, where

$$\Delta PA = PA(Y{-}ArCOOH) - PA(ArCOOH) \quad (3)$$

Measure of a substituent effect is usually effectively predicted by Hammett constants (Hammett, 1937). Fig. 4 shows PA = $f(\sigma_p)$ dependence, where σ_p are Hammett constants. The Hammett equation (and its extended forms) represents one of the most widely used means for the study and interpretation of organic reactions and their mechanisms. (Hansch et al., 1991; Krygowski and Stępień, 2005).
Linear regression provided these equations:

$$PA(B3LYP/IEF\text{-}PCM)/kJ \cdot mol^{-1} = 194.6 - 18.9\sigma_p \quad (4)$$

$$PA(B3LYP/SMD)/kJ \cdot mol^{-1} = 115.5 - 13.6\sigma_p \quad (5)$$

$$PA(M062X/IEF\text{-}PCM)/kJ \cdot mol^{-1} = \\ = 190.2 - 16.7\sigma_p \quad (6)$$

$$PA(M062X/SMD)/kJ \cdot mol^{-1} = 110.2 - 11.7\sigma_p \quad (7)$$

with the correlation coefficients for B3LYP/IEF-PCM of 0.982 and B3LYP/SMD 0.989, for M062X/IEF-PCM of 0.986 and M062X/SMD 0.982. Correlation of Hammett constants with gas phase PAs of *para*-substituted benzoic acids yielded correlation coefficient 0.979. In the present case, the selection of the functional led to only small changes of the intercept, which is much more sensitive to the choice of the solvation model. SMD model provides ca 80 $kJ \cdot mol^{-1}$ lower PAs in water than IEF-PCM model. Obtained intercepts as well as line slopes are lower than those found for the gas phase. Thus we can assume that aqueous solution induces considerable changes in the substituent effect in comparison to the gas phase.

Conclusion

In this paper the first step of SPLET mechanism was investigated for 15 selected monosubstitued benzoic acid derivatives in solution phase. Therefore the corresponding reaction enthalpy, proton affinity (PA), was evaluated for the carboxylate or phenoxide anions. Employing M062X and B3LYP functional in combination with the 6-311++G** basis set and IEF-PCM or SMD solvation models we were able to find that the theoretical PA values are more influenced by the choice of the solvation model. The presence of electron-donating substituents resulted, in general, in higher PA values while electron-withdrawing groups cause the decrease of PAs. Linearity for all functional and solvation model combinations of the corresponding Hammett type dependencies can be considered satisfactorily. In terms of the obtained PA values, OH group deprotonation was found to be thermodynamically preferred in salicylic acid. Future studies will investigate solution phase PAs of additional species employing a chemical microsolvation method.

References

Abramson R, Baldridge A, Kim K (2013) Journal of Chemical Theory and Computation 9: 1027—1035.

Andjelković M et al. (2006) Food Chemistry 98: 23—31.

Atkins PW (1998) Physical chemistry, 6th ed., Oxford University Press, Oxford.

Barberán FA, Clifford MN (2000) Journal of the Science of Food and Agriculture 80: 1024—1032.

Bordwell FG et al. (1994) Journal of the American Chemical Society 116: 6605—6610.

Cances E, Mennucci B, Tomasi J (1997) J. Chem. Phys 107: 3032—3041.

Cuvelier M-E, Richard H, Berset C (1992) Bioscience, biotechnology, and biochemistry 56: 324—325.

Dueñas M et al. (2011) European Food Research and Technology 232: 103—111.

Dumont E, Chaquin P (2009) The Journal of Physical Chemistry A 113: 2990—2994.

Galaverna RS et al. (2015) European Journal of Organic Chemistry 2015: 2189—2196.

Hammett LP (1937) J. Am. Chem. Soc. 59: 96—103.

Herrmann K, Nagel CW (1989) Critical Reviews in Food Science & Nutrition 28: 315—347.

Klein E, Lukeš V (2006) The Journal of Physical Chemistry A 110: 12312—12320.

Klein E, Rimarčík J, Lukeš V (2009) Acta Chim. Slovaca 2: 37—51.

Manach C et al. (2004) The American journal of clinical nutrition 79: 727—747.

Marenich AV, Cramer CJ, Truhlar DG (2009) The Journal of Physical Chemistry B 113: 6378—6396.

Pietta P-G (2000) Journal of natural products 63: 1035—1042.

Škorňa P et al. (2015) Acta Chimica Slovaca 8: 70—77.

Taft RW (1983) Prog. Phys. Org. Chem 14: 247—350.

Zhang B et al. (2015) Food chemistry 170: 226—233.

Zhao Y, Truhlar DG (2008) Theor. Chem. Acc. 120: 215—241.